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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)

REC'D 04 APR 2005

Applicant's or agent's file reference FP18807	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/001588	International Filing Date (day/month/year) 28 November 2003	Priority Date (day/month/year) 29 November 2002
International Patent Classification (IPC) or national classification and IPC Int. Cl. ⁷ C07H 15/234; A61K 31/7036; A61P 31/00		
Applicant BIOTA SCIENTIFIC MANAGEMENT PTY LTD et al		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.																
2.	This REPORT consists of a total of 5 sheets, including this cover sheet. <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 19 sheet(s).																
3.	This report contains indications relating to the following items: <table style="width: 100%; border: none;"> <tr> <td style="width: 5%;">I</td> <td><input checked="" type="checkbox"/> Basis of the report</td> </tr> <tr> <td>II</td> <td><input type="checkbox"/> Priority</td> </tr> <tr> <td>III</td> <td><input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td>IV</td> <td><input type="checkbox"/> Lack of unity of invention</td> </tr> <tr> <td>V</td> <td><input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td>VI</td> <td><input type="checkbox"/> Certain documents cited</td> </tr> <tr> <td>VII</td> <td><input type="checkbox"/> Certain defects in the international application</td> </tr> <tr> <td>VIII</td> <td><input checked="" type="checkbox"/> Certain observations on the international application</td> </tr> </table>	I	<input checked="" type="checkbox"/> Basis of the report	II	<input type="checkbox"/> Priority	III	<input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	IV	<input type="checkbox"/> Lack of unity of invention	V	<input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	VI	<input type="checkbox"/> Certain documents cited	VII	<input type="checkbox"/> Certain defects in the international application	VIII	<input checked="" type="checkbox"/> Certain observations on the international application
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Date of submission of the demand 24 June 2004	Date of completion of the report 7 March 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer <i>S. Chatterjee</i> SWARUP CHATTERJEE Telephone No. (02) 6283 2259

I. Basis of the report**1. With regard to the elements of the international application:***

- ☐ the international application as originally filed.
- ☒ the description, pages 1, 3-68, as originally filed,
pages , filed with the demand,
pages 2, 2a, 2b, received on 25 February 2005 with the letter of 25 February 2005
- ☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages 69-84 , received on 25 February 2005 with the letter of 25 February 2005
- ☐ the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims 1-37, 41-43, 48-51, 52, 55-70, 74-76, 81-85, 88-103	YES
	Claims 38-40, 44-47, 53, 54, 71-73, 77-80, 86, 87, 104, 105	NO
Inventive step (IS)	Claims 1-37, 43, 48-52, 55-62, 67, 76, 81-85, 88-95, 98-100	YES
	Claims 38-42, 44-47, 53, 54, 63-66, 68-75, 77-80, 86, 87, 96, 97 and 101-105	NO
Industrial applicability (IA)	Claims 1-105	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The following documents, also cited in the ISR, are considered for the purposes of this opinion:

D1 Nakagawa S et al., Microbial Drug Resistance, 1976, 2, 269-272
D2 Nakagawa S et al., Journal of Antibiotics, 1978, 31(7), 675-680
D3 US 3940382 (Unezawa et al.) 24 February 1976
D4 US 4347354 (Cron et al.) 31 August 1982
D5 Abe Y. et al., Journal of Antibiotics, 1977, 30(11), 1004-1007
D6 US 4020269 (Hiraga et al.) 26 April 1977
D7 US 4027332 (Fenner et al.) 17 May 1977

D1 (compounds 11-13) and D2 (compounds 11-13) disclose N-acylated kanamycin derivatives in which the 1-N, 3-N, 6'-N and 3"-N positions of kanamycin A contain a radical of the formula $C(O)CH(OH)CH_2CH_2NH_2$. D3 discloses kanamycin derivatives in which the 1-N position is modified with either $C(O)CH(OH)CH_2CH_2NH_2$ or $C(O)CH(OH)CH_2NH_2$ (column 6 line 37-7 line 2). These compounds fall within the scope of formula 1 in Claim 1 when $CH_2CH_2NH_2$ or CH_2NH_2 is Y and the carbamate linkage is L. Consequently, D1-D3 anticipate claims 38-40, 44-47, 53, 54, 71-73, 77-80, 86, 87, 104, 105 of the present application.

Claims 63-66, 68-70, 96-97 and 101-103 are considered to lack an inventive step in the light of D1-D3 as methods of treatment and use of such compounds would be obvious and routine to the person skilled in the art. Furthermore, claims 41, 42, 74 and 75 are considered to lack an inventive step as the carbamate linker is a technical equivalent of amide and imine linkers.

Claims 1-37, 43, 48-51, 52, 55-70, 76, 81-85, 88-103 are considered novel and inventive in the light of these citations as they do not disclose or suggest the matter defined within the claims.

D4 discloses 1-N-[ω -amino- α -hydroxyalkanoyl]aminoglycoside antibiotics (Claim 1 and examples). D4 anticipates Claims 38-40, 44-47, 53, 54, 71-73, 77-80, 86, 87, 104, 105 of the present application. Claims 63-66, 68-70, 96-97 and 101-103 are considered to lack an inventive step in the light of D4 as methods of treatment and use of such compounds would be obvious and routine to the person skilled in the art. Claims 41, 42, 74 and 75 also lack an inventive step as the carbamate linker is a technical equivalent of amide and imine linkers.

Claims 1-37, 43, 48-51, 52, 55-70, 76, 81-85, 88-103 are considered novel and inventive in the light of D4 as it does not disclose or suggest the matter defined within the claims.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims of the present application are not fully supported by the description. The exemplified matter is directed to tobramycin prodrugs. Claim 1, however, defines a prodrug where X' is any pharmaceutically active moiety (formula III); claim 38 defines X and X' as being an aminoglycoside excluding tobramycin (formulae I, II and III); claim 73 defines X and X' as a range of groups which find no support in the description. In each case the moieties are modified by a linker group and pharmacokinetic regulator. The generation of prodrugs from an active compound is a well known and accepted developmental tool for enhancing the bioavailability and pharmacokinetic profile of a specific compound. The term pharmacokinetic regulator is of indefinite scope since any modification to a compound will influence the pharmacokinetics of that compound and the release of the active compound from its prodrug formulation.

Consequently, Claims 1-4, 6-105 are not fully supported by the description. It is considered that the only real support in the description is for tobramycin prodrugs. It is noted that the search was restricted and was based on the exemplified matter because of the scope of the claims.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V.

D5 discloses benzyloxycarbonylkanamycin derivatives (chart 1) which fall within in the scope of formula I, in which the benzyl group is a pharmacokinetic regulator and the carbamate linker is L. Consequently, D5 anticipates claims 38-40, 44-47, 54, 71, 73, 77-80, 87 and 104. Claims 41, 42, 74 and 75 are considered to lack an inventive step as the carbamate linker is a technical equivalent of amide and imine linkers. Claims 1-37, 43, 48-53, 55-70, 72, 76, 81-86, 88-103 and 105 are considered to be novel and inventive in the light of this citation.

D6 discloses 3' phosphorylated aminoglycosides (reference examples 2-6). D6 anticipates claims 38-40, 44, 73 and 77 of the present application because of the breadth of the definitions of linker and pharmacokinetic regulator. Claims 1-37, 41-43, 45-72, 74-76 and 78-105 are novel and inventive in the light of D6 as this document does not disclose or suggest the matter defined within these claims.

D7 discloses modified kanamycin compounds in which t-boc and MeOC(O) are located at the 6'-N position (Claim 20 and column 14 lines 1-59). D7 anticipates claims 38-40, 44-47, 53, 54, 71-73, 77-80, 86, 87, 104, and 105 of the present application. Claims 63-66, 68-70, 96-97 and 101-103 are considered to lack an inventive step in the light of D7 as methods of treatment and use of such compounds would be obvious and routine to the person skilled in the art. Claims 41, 42, 74 and 75 are considered to lack an inventive step as the carbamate linker is a technical equivalent of amide and imine linkers. Claims 1-37, 43, 48-52, 55-62, 67, 76, 81-85, 88-95 and 98-100 are considered novel and inventive in the light D7 as they do not disclose or suggest the matter defined within the claims.

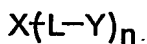
The matter defined within Claims 1-105 is considered to be industrially applicable.

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targeting groups (labile or otherwise) could also be attached to the prodrug to enhance the delivery process.

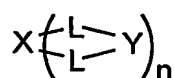
In a first aspect, the present invention provides a prodrug of the general Formula (I), (II) or (III):

5



(I)

10



(II)

15



(III)

in which

X is a tobramycin moiety;

X' is a pharmaceutically active moiety;

L is a linker group;

20

Y is a pharmacokinetic regulator; and

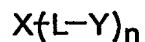
n is an integer of 1 or greater

or a pharmaceutically acceptable derivative or salt

thereof.

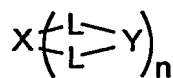
The invention also provides a prodrug of general Formula (I), (II) or (III):

25



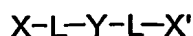
(I)

30



(II)

35



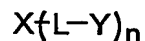
(III)

- 2a -

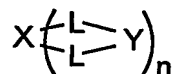
in which

5 X and X' are either the same or different and
 selected from an aminoglycoside excluding tobramycin;
 L is a linker group excluding amide and carbamate;
 Y is a pharmacokinetic regulator; and
 n is an integer of 1 or greater
 10 or a pharmaceutically acceptable derivative or salt
 thereof.

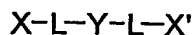
The invention further provides a prodrug of the
 general Formula (I), (II) or (III):



15 (I)



20 (II)



(III)

in which

25 X and X' are either the same or different and
 selected from a nucleoside, rhinovirus capsid-binding
 compound, antisense oligonucleotide, peptide, an inhibitor of
 HIVRT, an inhibitor of influenza neuraminidase, amphotericin
 30 β , an azole and an aspartic proteinase;

L is a linker group;
 Y is a pharmacokinetic regulator; and
 n is an integer of 1 or greater
 or a pharmaceutically acceptable derivative or salt
 35 thereof.

- 2b -

In a second aspect, the present invention provides a method for the preparation of the prodrug as defined above which comprises the steps of:

- 5 (a) optionally protecting the pharmaceutically active moieties X and/or X' and/or the linker group which is attached to the optionally protected pharmacokinetic regulator Y;
- 10 (b) reacting the optionally protected pharmaceutically active moieties X and/or X' and the optionally protected linker group L attached to the optionally protected pharmacokinetic regulator Y; and
- (c) if necessary, removing the protecting groups of the pharmaceutically active moieties X and/or X', the linker L and the pharmacokinetic regulator Y.

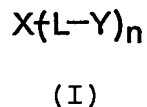
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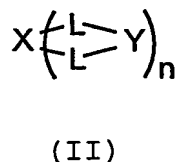
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A prodrug of the general Formula (I), (II) or (III):

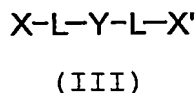
5



10



15



in which

- X is a tobramycin moiety;
 X' is a pharmaceutically active moiety;
 L is a linker group;
 20 Y is a pharmacokinetic regulator; and
 n is an integer of 1 or greater
 or a pharmaceutically acceptable derivative or
 salt thereof.

- 25 2. A prodrug according to claim 1, in which the
 pharmaceutically active moiety is selected from an
 aminoglycoside, nucleoside, rhinovirus capsid-binding
 compound, antisense oligonucleotide, peptide, an inhibitor
 of HIVRT, an inhibitor of influenza neuraminidase,
 30 amphotericin β , an azole and an aspartic proteinase.

3. A prodrug according to claim 2, in which the
 aminoglycoside is selected from tobramycin, kanamycin A to
 C, amikacin, neomycin, streptomycin, neamine, paromomycin,
 35 lividomycin, 2230-C, ribostamycin, xyllostasin, butirosin,
 4'-deoxybutyrosin, LL-BM408a, gentamycins and nebramycin.

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4. A prodrug according to claim 3, in which the aminoglycoside is tobramycin, amikacin, neomycin or kanamycin.
- 5 5. A prodrug according to claim 3 or claim 4, in which the aminoglycoside is tobramycin.
6. A prodrug according to any one of claims 1 to 5, in which the linker group is selected from esters, amides, ureas, thioureas, imines, acetals, ethers, phosphates, phosphate esters or diesters, thioesters, oximes and hydrazones.
- 10 7. A prodrug according to claim 6, in which the linker group is selected from an ester, amide, oxime and phosphate.
- 15 8. A prodrug according to any one of claims 2 to 7, in which the linker group is an ester.
- 20 9. A prodrug according to any one of the preceding claims, in which the pharmacokinetic regulator Y is a hydrophobic or hydrophilic moiety.
- 25 10. A prodrug according to claim 9, in which the hydrophobic moiety is an optionally substituted straight chain, branched and/or cyclic saturated or unsaturated hydrocarbon.
- 30 11. A prodrug according to claim 10, in which the hydrophobic moiety is an optionally substituted alkyl or optionally substituted alkenyl having 1 to 24 carbon atoms which is optionally interrupted with oxygen or nitrogen; optionally substituted aryl; or an optionally substituted heterocyclyl.
- 35 12. A prodrug according to claim 11, in which the optionally substituted alkyl or optionally substituted alkenyl is optionally substituted C₁₋₂₀ alkyl or optionally

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substituted C₂₋₂₀ alkenyl which is optionally interrupted with O, C=O, NH, optionally substituted aryl or optionally substituted heterocyclyl and optionally substituted with carboxyl, optionally substituted C₁₋₆ alkyl, amino or hydroxyl.

13. A prodrug according to claim 11, in which the optionally substituted aryl is an optionally substituted phenyl or optionally substituted biphenyl.

14. A prodrug according to claim 11, in which the optionally substituted heterocyclyl is a 5- or 6-membered nitrogen containing heterocyclic group.

15. A prodrug according to claim 14, in which the heterocyclic group is selected from pyridyl, indolyl, indazolyl, 2,3-dihydro-1H-indolyl, furanyl, isoxazolyl, pyrazolyl and thiofuranyl.

16. A prodrug according to any one of claims 13 to 15, in which the optional substituents on the phenyl or heterocyclyl are selected from halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, hydroxy and OCF₃.

17. A prodrug according to claim 9, in which the hydrophilic moiety is selected from oligonucleotides up to 20 nucleotides in length, peptides up to 20 amino acids in length, peptide mimics, carbohydrates, oligosaccharides and derivatives thereof.

18. A method for the preparation of the prodrug as defined in any one of claims 1 to 17, which comprises the steps of:

(a) optionally protecting the moieties X and/or X' and/or the linker group which is attached to the optionally protected pharmacokinetic regulator Y;

(b) reacting the optionally protected moieties X and/or X' and the optionally protected linker group L

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attached to the optionally protected pharmacokinetic regulator Y; and

(c) if necessary, removing the protecting groups of the moieties X and/or X', the linker L and the
5 pharmacokinetic regulator Y.

19. A pharmaceutical formulation comprising the prodrug as defined in any one of claims 1 to 17 or a pharmaceutically acceptable salt or derivative thereof,
10 together with one or more pharmaceutically acceptable carriers.

20. A pharmaceutical formulation according to claim19, which further comprises one or more other
15 therapeutic and/or prophylactic ingredients.

21. A pharmaceutical formulation according to claim20, in which the other therapeutic and/or prophylactic ingredient is an antimicrobial or
20 antiinfective agent.

22. A pharmaceutical formulation according to claim21, in which the antiinfective agent is an antibacterial agent.
25

23. A pharmaceutical formulation according to claim22, in which the antibacterial agent is used to treat respiratory infections.

30 24. A pharmaceutical formulation according to claim 22 or claim23, in which the antibacterial agent is a combination of trimethoprim and sulfonamide; bacitracin and polymyxin B-neomycin; imipenem and fluoroquinolone; and beta-lactam and aminoglycosides.

35 25. An inhaler which comprises a prodrug as defined in any one of claims 1 to 17 or a formulation as defined in any one of claims 19 to24.

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26. An inhaler according to claim 25 which is adapted for oral administration as a free-flow powder.

27. An inhaler according to claim 25 which is a
5 metered dose aerosol inhaler.

28. A method for the prevention and/or treatment of a microbial infection comprising the step of administration to a subject in need thereof of an
10 effective amount of the prodrug as defined in any one of claims 1 to 17 or a formulation as defined in any one of claims 19 to 24.

29. A method according to claim 28, in which the
15 microbial infection is a bacterial infection.

30. A method according to claim 29, in which the bacterial infection is a Gram Negative or Gram Positive infection.
20

31. A method according to claim 30, in which the bacterial infection is associated with the respiratory tract, urinary tract or GI tract or a systemic infection caused by enteric bacteria.
25

32. A method according to any one of claims 28 to 31 in which the administration is to the respiratory tract by inhalation, insufflation or intranasally or a combination thereof.
30

33. Use of the prodrug as defined in any one of claims 1 to 17 for the manufacture of a medicament for the prevention and/or treatment of a microbial infection.

34. Use of the prodrug as defined in any one of claims 1 to 17 in the prevention and/or treatment of a microbial infection.
35

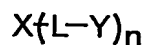
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35. Use of the prodrug as defined in any one of claims 1 to 17 as an antimicrobial agent.

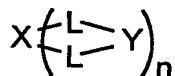
36. A prodrug as defined in any one of claims 1 to 17 or a formulation as defined in any one of claims 19 to 24 for use in the prevention and/or treatment of a microbial infection.

37. A method for the detection of a microbial infection which comprises the step of contacting the prodrug as defined in any one of claims 1 to 17 or the formulation as defined in any one of claims 19 to 24 with a sample suspected of containing the microorganism.

38. A prodrug of general Formula (I), (II) or (III):



(I)



(II)



(III)

in which

X and X' are either the same or different and selected from an aminoglycoside excluding tobramycin;

L is a linker group excluding amide and carbamate;

Y is a pharmacokinetic regulator; and

n is an integer of 1 or greater

or a pharmaceutically acceptable derivative or salt thereof.

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39. A prodrug according to claim 38, in which the aminoglycoside X is selected from kanamycin A to C, amikacin, neomycin, streptomycin, neamine, paromomycin, lividomycin, 2230-C, ribostamycin, xyllostasin, butirosin, 4'-deoxybutyrosin, LL-BM408a, gentamycins and nebramycin.
40. A prodrug according to claim 39, in which the aminoglycoside is amikacin, neomycin or kanamycin.
41. A prodrug according to any one of claims 38 to 40, in which the linker group is selected from esters, ureas, thioureas, imines, acetals, ethers, phosphates, phosphate esters or diesters, thioesters, oximes and hydrazones.
42. A prodrug according to claim 41, in which the linker group is selected from an ester, oxime and phosphate.
43. A prodrug according to claim 41 or claim 42, in which the linker group is an ester.
44. A prodrug according to any one of claims 38 to 43, in which the pharmacokinetic regulator is a hydrophobic or hydrophilic moiety.
45. A prodrug according to claim 44, in which the hydrophobic moiety is an optionally substituted straight chain, branched and/or cyclic saturated or unsaturated hydrocarbon.
46. A prodrug according to claim 45, in which the hydrophobic moiety is an optionally substituted alkyl or optionally substituted alkenyl having 1 to 24 carbon atoms which is optionally interrupted with oxygen or nitrogen; optionally substituted aryl; or an optionally substituted heterocyclyl.

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47. A prodrug according to claim 46, in which the optionally substituted alkyl or optionally substituted alkenyl is optionally substituted C₁₋₂₀ alkyl or optionally substituted C₂₋₂₀ alkenyl which is optionally interrupted
5 with O, C=O, NH, optionally substituted aryl or optionally substituted heterocyclyl and optionally substituted with carboxyl, optionally substituted C₁₋₆ alkyl, amino or hydroxyl.
- 10 48. A prodrug according to claim 46, in which the optionally substituted aryl is an optionally substituted phenyl or optionally substituted biphenyl.
- 15 49. A prodrug according to claim 46, in which the optionally substituted heterocyclyl is a 5- or 6-membered nitrogen containing heterocyclic group.
- 20 50. A prodrug according to claim 49, in which the heterocyclic group is selected from pyridyl, indolyl, indazolyl, 2,3-dihydro-1H-indolyl, furanyl, isoxazolyl, pyrazolyl and thiofuranyl.
- 25 51. A prodrug according to any one of claims 48 to 50, in which the optional substituents on the phenyl or heterocyclyl are selected from halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, hydroxy and OCF₃.
- 30 52. A prodrug according to claim 44, in which the hydrophilic moiety is selected from oligonucleotides up to 20 nucleotides in length, peptides up to 20 amino acids in length, peptide mimics, carbohydrates, oligosaccharides and derivatives thereof.
- 35 53. A method for the preparation of the prodrug as defined in any one of claims 38 to 51, which comprises the steps of:
- (a) optionally protecting the moieties X and/or X' and/or the linker group which is attached to the optionally protected pharmacokinetic regulator Y;

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(b) reacting the optionally protected moieties X and/or X' and the optionally protected linker group L attached to the optionally protected pharmacokinetic regulator Y; and

5 (c) if necessary, removing the protecting groups of the moieties X and/or X', the linker L and the pharmacokinetic regulator Y.

10 54. A pharmaceutical formulation comprising the prodrug as defined in any one of claims 38 to 52 or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers.

15 55. A pharmaceutical formulation according to claim 54, which further comprises one or more other therapeutic and/or prophylactic ingredients.

20 56. A pharmaceutical formulation according to claim 55, in which the other therapeutic and/or prophylactic ingredient is an antimicrobial or antiinfective agent.

25 57. A pharmaceutical formulation according to claim 56, in which the antiinfective agent is an antibacterial agent.

30 58. A pharmaceutical formulation according to claim 57, in which the antibacterial agent is used to treat respiratory infections.

35 59. A pharmaceutical formulation according to claim 57 or claim 58, in which the antibacterial agent is a combination of trimethoprim and sulfonamide; bacitracin and polymyxin B-neomycin; imipenem and fluoroquinolone; and beta-lactam and aminoglycosides.

60. An inhaler which comprises a prodrug as defined in any one of claims 38 to 52 or a formulation as defined in any one of claims 54 to 59.

61. An inhaler according to claim 60 which is adapted for oral administration as a free-flow powder.
- 5 62. An inhaler according to claim 60 which is a metered dose aerosol inhaler.
63. A method for the prevention and/or treatment of a microbial infection comprising the step of
10 administration to a subject in need thereof of an effective amount of the prodrug as defined in any one of claims 38 to 52 or a formulation as defined in any one of claims 54 to 59.
- 15 64. A method according to claim 63, in which the microbial infection is a bacterial infection.
65. A method according to claim 64, in which the bacterial infection is a Gram Negative or Gram Positive
20 infection.
66. A method according to claim 65, in which the bacterial infection is associated with the respiratory tract, urinary tract or GI tract or a systemic infection
25 caused by enteric bacteria.
67. A method according to any one of claims 63 to 66 in which the administration is to the respiratory tract by inhalation, insufflation or intranasally or a combination
30 thereof.
68. Use of the prodrug as defined in any one of claims 38 to 51 for the manufacture of a medicament for the prevention and/or treatment of a microbial infection.
35
69. Use of the prodrug as defined in any one of claims 38 to 51 in the prevention and/or treatment of a microbial infection.

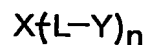
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70. Use of the prodrug as defined in any one of claims 38 to 51 as an antimicrobial agent.

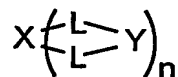
71. A prodrug as defined in any one of claims 38 to 51 or a formulation as defined in any one of claims 54 to 59 for use in the prevention and/or treatment of a microbial infection.

72. A method for the detection of a microbial infection which comprises the step of contacting the prodrug as defined in any one of claims 38 to 51 or the formulation as defined in any one of claims 54 to 59 with a sample suspected of containing the microorganism.

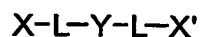
73. A prodrug of the general Formula (I), (II) or (III):



(I)



(II)



(III)

in which

X and X' are either the same or different and selected from a nucleoside, rhinovirus capsid-binding compound, antisense oligonucleotide, peptide, an inhibitor of HIVRT, an inhibitor of influenza neuraminidase, amphotericin β , an azole and an aspartic proteinase;

L is a linker group;

Y is a pharmacokinetic regulator; and

n is an integer of 1 or greater

or a pharmaceutically acceptable derivative or salt thereof.

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74. A prodrug according to claim 73, in which the linker group is selected from esters, amides, ureas, thioureas, imines, acetals, ethers, phosphates, phosphate esters or diesters, thioesters, oximes and hydrazones.

5

75. A prodrug according to claim 74, in which the linker group is selected from an ester, amide, oxime and phosphate.

10 76. A prodrug according to claim 74 or claim 75, in which the linker group is an ester.

77. A prodrug according to any one of claims 73 to 76, in which the pharmacokinetic regulator is a
15 hydrophobic or hydrophilic moiety.

78. A prodrug according to claim 77, in which the hydrophobic moiety is an optionally substituted straight chain, branched and/or cyclic saturated or unsaturated
20 hydrocarbon.

79. A prodrug according to claim 78, in which the hydrophobic moiety is an optionally substituted alkyl or optionally substituted alkenyl having 1 to 24 carbon atoms
25 which is optionally interrupted with oxygen or nitrogen; optionally substituted aryl; or an optionally substituted heterocyclyl.

80. A prodrug according to claim 79, in which the optionally substituted alkyl or optionally substituted alkenyl is optionally substituted C₁₋₂₀ alkyl or optionally substituted C₂₋₂₀ alkenyl which is optionally interrupted with O, C=O, NH, optionally substituted aryl or optionally substituted heterocyclyl and optionally substituted with
30 carboxyl, optionally substituted C₁₋₆ alkyl, amino or
35 hydroxyl.

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81. A prodrug according to claim 79, in which the optionally substituted aryl is an optionally substituted phenyl or optionally substituted biphenyl.
- 5 82. A prodrug according to claim 79, in which the optionally substituted heterocyclyl is a 5- or 6-membered nitrogen containing heterocyclic group.
- 10 83. A prodrug according to claim 82, in which the heterocyclic group is selected from pyridyl, indolyl, indazolyl, 2,3-dihydro-1H-indolyl, furanyl, isoxazolyl, pyrazolyl and thiofuranyl.
- 15 84. A prodrug according to any one of claims 81 to 83, in which the optional substituents on the phenyl or heterocyclyl are selected from halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, hydroxy and OCF₃.
- 20 85. A prodrug according to claim 77, in which the hydrophilic moiety is selected from oligonucleotides up to 20 nucleotides in length, peptides up to 20 amino acids in length, peptide mimics, carbohydrates, oligosaccharides and derivatives thereof.
- 25 86. A method for the preparation of the prodrug as defined in any one of claims 73 to 85, which comprises the steps of:
- 30 (a) optionally protecting the moieties X and/or X' and/or the linker group which is attached to the optionally protected pharmacokinetic regulator Y;
- (b) reacting the optionally protected moieties X and/or X' and the optionally protected linker group L attached to the optionally protected pharmacokinetic regulator Y; and
- 35 (c) if necessary, removing the protecting groups of the moieties X and/or X', the linker L and the pharmacokinetic regulator Y.

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87. A pharmaceutical formulation comprising the prodrug as defined in any one of claims 73 to 85 or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers.

88. A pharmaceutical formulation according to claim 87, which further comprises one or more other therapeutic and/or prophylactic ingredients.

89. A pharmaceutical formulation according to claim 88, in which the other therapeutic and/or prophylactic ingredient is an antimicrobial or antiinfective agent.

90. A pharmaceutical formulation according to claim 89, in which the antiinfective agent is an antibacterial agent.

91. A pharmaceutical formulation according to claim 90, in which the antibacterial agent is used to treat respiratory infections.

92. A pharmaceutical formulation according to claim 90 or claim 91, in which the antibacterial agent is a combination of trimethoprim and sulfonamide; bacitracin and polymyxin B-neomycin; imipenem and fluoroquinolone; and beta-lactam and aminoglycosides.

93. An inhaler which comprises a prodrug as defined in any one of claims 73 to 85 or a formulation as defined in any one of claims 87 to 92.

94. An inhaler according to claim 93 which is adapted for oral administration as a free-flow powder.

95. An inhaler according to claim 93 which is a metered dose aerosol inhaler.

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96. A method for the prevention and/or treatment of a microbial infection comprising the step of administration to a subject in need thereof of an effective amount of the prodrug as defined in any one of claims 73 to 85 or a formulation as defined in any one of claims 87 to 92.

97. A method according to claim 96, in which the microbial infection is a viral, fungal, parasitic, yeast or protozoal infection.

98. A method according to claim 97, in which the viral infection is an orthomyxovirus or paramyxovirus infection.

99. A method according to claim 97 or claim 98 in which the viral infection is an influenza A or B infection, parainfluenza, mumps or Newcastle disease.

100. A method according to any one of claims 96 to 99 in which the administration is to the respiratory tract by inhalation, insufflation or intranasally or a combination thereof.

101. Use of the prodrug as defined in any one of claims 73 to 85 for the manufacture of a medicament for the prevention and/or treatment of a microbial infection.

102. Use of the prodrug as defined in any one of claims 73 to 85 in the prevention and/or treatment of a microbial infection.

103. Use of the prodrug as defined in any one of claims 73 to 85 as an antimicrobial agent.

104. A prodrug as defined in any one of claims 73 to 85 or a formulation as defined in any one of claims 87 to 92 for use in the prevention and/or treatment of a microbial infection.

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105. A method for the detection of a microbial
infection which comprises the step of contacting the
prodrug as defined in any one of claims 73 to 85 or the
5 formulation as defined in any one of claims 87 to 92 with
a sample suspected of containing the microorganism.